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Data Article

Ethoxycarbonyl functionalized Tröger's base alongside its congener dihydroquinazoline: A trick with crystallization

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ABSTRACT

The synthesis of ethoxycarbonyl functionalized Tröger's base is accompanied by the formation of a considerable amount of a 3,4-dihydroquinazoline by-product. We found that both compounds can be readily isolated from reaction mixture on a preparative scale by standard crystallization from appropriate solvents.

Specifications table

Subject area	*Organic chemistry*
Compounds	*2,8-Bis(ethoxycarbonyl)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine; Ethyl 3-[4-(ethoxycarbonyl)phenyl]-3,4-dihydroquinazoline-6-carboxylate*
Data category	*Spectral, synthesized, crystallographic, melting points*
Data acquisition format	*NMR, IR, MS, XRD*
Data type	*Analyzed*
Procedure	*Chemical transformations, purification*
Data accessibility	*Provided with this article*

1. Rationale

Since the first synthesis by Julius Tröger [1], Tröger's bases continue to fascinate chemists due to their unique structural properties and reactivity. They find a growing number of applications in a variety of domains including supramolecular systems, metallo complexes, polymers, studying important aspects of stereochemistry [2–5]. Herein, we focused on the multigram synthesis of the ester-functionalized Tröger's base **1** (Scheme 1) being of interest to us as a promising object for further chiral resolution. This molecule was used previously for the construction of coordination polymers [6] and receptors which selectively bind dicarboxylic acids [7,8].

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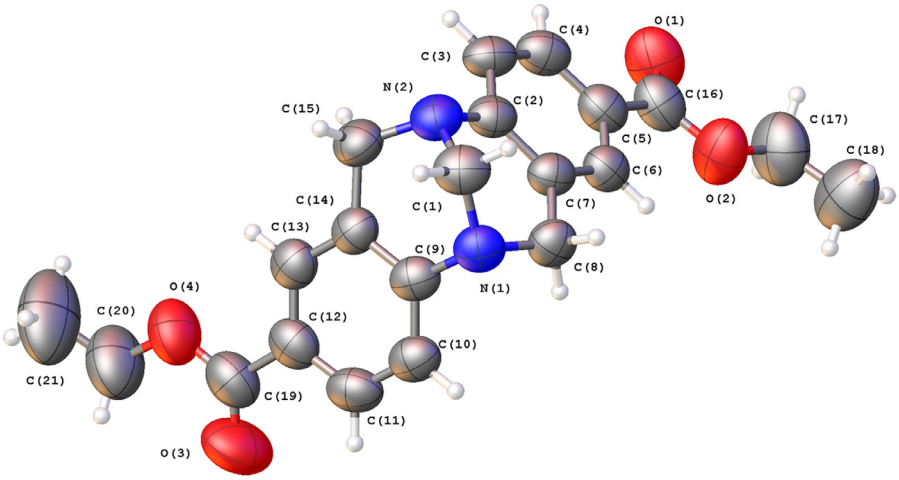
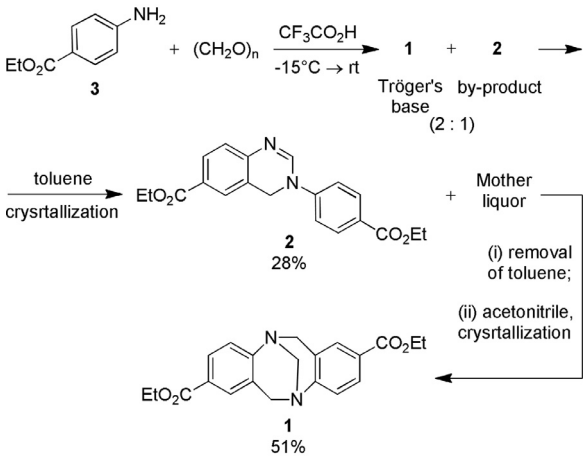


Fig. 1. Molecular structure of compound **1**.



Scheme 1. Synthesis of Tröger base **1** and dihydroquinazoline **2**.

According to several thorough studies [9–11], condensation of anilines with paraformaldehyde in a trifluoroacetic acid medium is the method of choice to obtain structural analogues of Tröger's base. This process could be complicated by the formation of unreactive 3,4-dihydroquinazoline semi-products which terminate further reaction sequences [12]. This happens, especially, in the case of anilines with electron withdrawing substituents. It is worth to note that dihydroquinazolines themselves form another diverse family of highly potent nitrogen heterocycles [13–15].

We performed the synthesis of Tröger's base **1** following the Sergeyev et al. procedure [10], having obtained a mixture of target compound **1** and by-product dihydroquinazoline **2** in a poor ratio 2:1 (Scheme 1). Variation of the reaction temperature and aniline **3**/paraformaldehyde ratio, or longer reaction time did not improve the yield of **1**. In the work [11] this difficulty was circumvented by utilizing *orto* substituted anilines and esters with longer alkyl chain. In an effort to develop a more preparative procedure for **1**, we found that compounds **1** and **2** demonstrate different solubility behavior (despite a structural similarity), and that they can be isolated selectively by crystallization from appropriate solvents. Apparently, dihydroquinazoline **2** fell out from toluene in a yield close to quantitative, while Tröger's base **1** remains soluble at room temperature. Once the solvent was replaced with acetonitrile, compound **1** crystallized perfectly.

Thus, through a manipulation with two solvents we isolated both high purity products on preparative scale and avoided time-consuming chromatography step [7,10,11,16]. The structures of **1** and **2** have been confirmed by spectroscopic methods. For compound **2**, X-ray crystal structure was determined previously [17]. Our paper reports crystallographic data for Tröger's base **1** (Fig. 1).

2. Procedure

IR spectra were recorded on a Vertex 70 spectrometer. MS analysis was performed using Agilent 6890 N/5975 GC/MS instrument in the electron impact ionization mode at 70 eV. ^{1}H NMR and ^{13}C NMR spectra were recorded at 500 MHz and

125 MHz respectively on a Bruker Avance 500 spectrometer. Chemical shifts were referred to the signals of residual DMSO (δ = 2.50 ppm in ^{1}H NMR and δ = 39.50 ppm in ^{13}C NMR). Elemental analysis was performed using Thermo Scientific TM Flash 2000 CHNS/O analyser. Crystal structure was determined with Oxford Diffraction Xcalibur, Ruby, Gemini Ultra diffractometer.

Synthesis and separation of compounds 1 and 2. Ethyl *p*-aminobenzoate (40.5 g, 245 mmol) was added portionwise to mechanically stirred trifluoroacetic acid (400 mL), which was placed prior in an ice-salt bath and cold to –15 °C. Once the addition was complete, the mixture was stirred for 15–20 min to lower slightly increased temperature. Whereupon paraformaldehyde (15.0 g, 500 mmol) was added portionwise, and stirring was continued for 16 h, meanwhile the mixture was gradually warmed to room temperature. The resulting mixture was evaporated in vacuum, the residue was treated consistently with crushed ice (500 g) and 25% ammonia solution (500 mL). The products were extracted with CH_2Cl_2 (4 × 250 mL). Combined organic extracts were washed with saturated solution of Na_2CO_3 (100 mL) and brine (100 mL), dried with Na_2SO_4, evaporated under reduced pressure. The residue was dissolved in refluxing toluene (200 mL), and transparent solution was left at room temperature. The solids formed were separated by filtration and washed with toluene (2 × 50 mL). Crystallization from toluene was repeated in the same manner giving pure compound **2** as pale yellow plates, yield 12.2 g (28%).

Mother liquor after first crystallization was concentrated in vacuum. The residue was twice recrystallized from of acetonitrile (120 and 130 mL, refrigerator) to afford pure Tröger's base **1** as colorless needles (15.9 g). Concentration and reprocessing of acetonitrile filtrates gave additional amounts of **1** (7.0 g). Total yield of **1**: 22.9 g (51%).

3. Data, value and validation

2,8-Bis(ethoxycarbonyl)-6H,12H-5,11-methanodibenzo[b,f][1,5]diazocine 1. Mp 155–156 °C (lit. [16] mp 152–153 °C). NMR and IR spectra were in agreement with reported [7,11,16].

Ethyl 3-[4-(ethoxycarbonyl)phenyl]-3,4-dihydroquinazoline-6-carboxylate 2. Mp 185–187 °C (lit. [11] mp 190–191 °C), IR (film), ν_{max}, cm^{-1}: 3388, 3076, 2980, 2904, 1691, 1631, 1591, 1558. ^{1}H NMR spectrum (500 MHz, DMSO–d_6), δ, ppm (J, Hz): 8.01 (2H, br d, J = 8.9, Ar); 7.95 (1H, s, CH=*N*); 7.81 (1H, dd, J = 8.2, J = 1.8, Ar); 7.75 (1H, br d, J = 1.8, Ar); 7.47 (2H, br d, J = 8.9, Ar); 7.16 (1H, d, J = 8.2, Ar); 5.06 (2H, s, ArC$\underline{H}_2$); 4.31 (2H, q, J = 7.1, $CH_3C\underline{H}_2O$); 4.29 (2H, q, J = 7.1, $CH_3C\underline{H}_2O$); 1.33 (3H, t, J = 7.0, CH_3), 1.31 (3H, t, J = 7.0, CH_3). ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 165.24 (C); 165.20 (C); 147.6 (CH); 145.8 (C); 145.1 (C); 130.5 (2CH); 129.6 (CH); 127.4 (CH); 126.5 (C); 125.0 (C); 124.2 (CH); 122.3 (C); 116.9 (2CH); 60.63 (CH_2); 60.58 (CH_2); 45.5 (CH_2); 14.2 (2CH_3). NMR spectra were similar to reported [11]. MS (ESI), *m/z*: 353.2 $[M + H]^+$.

Crystal data for 1. $C_{21}H_{22}N_2O_4$ (M 366.41), orthorhombic, $Pca2_1$, a = 10.2541(5), b = 22.8519(11) and c = 8.0645(3) Å, V = 1889.72(15) Å^3, Z = 4, d_{calc} = 1.288 g cm^{-3}, F(000) = 776. Single crystal (colorless needle, dimensions 0.029 × 0.067 × 0.65 mm) was selected and intensities of 5472 reflections were measured with Oxford Diffraction Xcalibur, Ruby, Gemini Ultra diffractometer at 295 K [ω scans, λ(Cu Ka) = 1.54184 Å, μ = 0.733 mm^{-1}, $2\theta_{max}$ = 134.456°]. Final R factors: R_1 = 0.0532 [2253 reflections with $I > 2\sigma(I)$], wR^2 = 0.1589 (all reflections), GOF = 1.030. The structure was solved with the SHELXT [18] and refined with the SHELXL-2016/6 program [19]. Molecular graphics were prepared using Olex2 program [20].

CCDC 1934607 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk.

The supplementary materials file containing copies of NMR spectra is available from the journal website.

Declaration of Competing Interest

None.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.cdc.2020.100339.

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